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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 3/17/03, as Paper No. 9. The amendment has been entered. Claim 1 has been amended. Claims 1-9 are presently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

1. Claims 1-9 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record (see the Office Action mailed 10/11/02).

As mentioned in the previous Office Action, the claims are drawn to a method of reducing tumor mass comprising administering to an individual suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that only one $\gamma_1$34.5 gene remains intact, said amount of HSV being effective to reduce tumor mass. (Emphasis added for clarity). As previously indicated, the claim encompasses administering an HSV comprising any modification in an inverted repeat region that results in only one $\gamma_1$34.5 gene

remaining intact. Therefore, the claims encompass an enormous number of different modified HSVs, considering every possible modification that could be made in an HSV inverted repeat region that would result in only one $\gamma_1$34.5 gene remaining intact. For instance, the claims encompass everything from a deletion of the entire inverted repeat region except for one of the two $\gamma_1$34.5 genes, to a single point mutation in one of the two $\gamma_1$34.5 genes remains; the only limitation being that one $\gamma_1$34.5 gene remains "intact". The specification, however, only describes one particular modification of an HSV inverted repeat region that results in only one $\gamma_1$34.5 gene remaining intact which has the desired functional characteristics described in the specification.

Response to Arguments

2. Applicant's arguments filed 3/17/03 have been fully considered but they are not persuasive.

3. Applicants argue that Examiner's reliance on The regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559 (Fed Cir. 1997) is misplaced because the Lilly case was drawn to a genus of compounds each having distinct structures wherein all of the structures had a common function, but the specification only described one structure having the function. Applicants argue that the instant case is not drawn to a genus of compounds having distinct structures, but rather the instant claims are drawn to methods. Applicants maintain that it is irrelevant whether there are thousands or even millions of different ways the HSV gene could be modified such that only one $\gamma_1$34.5 gene remains intact. Applicants assert that the issue is whether the Applicants were in possession of the invention drawn to methods of administering a modified HSV as of the effective filing date. Furthermore, Applicants contend that adequate

description does not require description of every species encompassed by the claims, only that the description is sufficient to allow one of ordinary skill in the art to recognize that the Applicant invented what is claimed (see p. 4 of the response filed 3/17/03).

In response, it is acknowledged that the claims are drawn to methods, not to a genus of distinct compounds, as in Lilly. However, it is respectfully pointed out that the claimed methods encompass the use of a genus of distinct compounds, each having different structures but all having a common function (i.e. the function being attenuated replication in normal cells compared to wild-type and with the ability to kill cancerous cells). Therefore, the reliance on Lilly is appropriate. Furthermore, it is not irrelevant that the claims encompass thousands, if not millions of different possible modified HSV because, as previously mentioned, the specification has only described one specific modified HSV that has the desired function. There is no description indicating which modifications in the HSV inverted repeat region which result in only one $\gamma_1$34.5 gene remaining intact have the required function. Furthermore, there is no indication of the critical regions or elements of the HSV inverted repeat region (other than the $\gamma_1$34.5 gene) that must be present in order for the HSV to have required the function. It is acknowledged that the issue is not whether all embodiments have been described. However, in order for a disclosure to meet the written description requirements, the disclosure must describe a "representative number" of species encompassed by the claims. Specifically, the revised guidelines for written description indicates, "[A] satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21,

1999 (Volume 64, Number 244), revised guidelines for written description). Here, as previously mentioned, the instant disclosure does no adequately describe a "representative number" of the modified HSVs encompassed by the claims. The specification only discloses one specific modified HSV having the desired function, without providing guidance on how to make other modified HSVs which would also have the desired function. Therefore, the rejection of claims 1-9 under 35 USC first paragraph (written description) is appropriate, and the rejection is not withdrawn.

It is noted that limiting the claims to the one modified HSV described in the specification would obviate this rejection. Specifically, amending the claim to limit the modified HSV to one consisting of a HSV lacking U_L24, U_L56 and further lacking one set of the inverted repeats encoding one copy of the genes $\alpha 0$, $\alpha 4$, $\gamma_1 34.5$, ORFP and ORFO (as described on p. 7, lines 26-30 of the specification) would obviate this rejection.

4. Additionally, claims 1-9 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record, because the specification, while being enabling for the reduction of tumor mass (i.e. treatment) by direct injection into a tumor using a specific attenuated HSV R7020 mutant (comprising the specific modification described in the specification wherein only one $\gamma_1 34.5$ gene remains intact), does not reasonably provide enablement for treatment in an individual via any route of administration other than direct injection and wherein the virus comprises any modification in an HSV inverted repeat region.

5. Applicant's arguments filed 3/17/03 have been fully considered but they are not fully persuasive. Specifically, Applicants arguments are persuasive to the extent that the treatment is

now deemed to be enabled not just for athymic nude mice, but also for all individuals suffering from cancer. However, the Applicants arguments with respect to the routes of administration and to the administration of any modified HSV encompassed by the claims (other than the one specifically described) are not persuasive.

Applicants acknowledge that the claims are not limited to any particular route of administration; however, Applicants maintain that the specification demonstrates an operative aspect of the invention against which all alternative aspects can be compared by routine optimization (see p. 3 of the response filed 3/17/03). The Applicants point to two different references "Kooby" and "Walker" (both published after the filing date of the instant application) which indicate that modified HSVs which do not express either of the two $\gamma_1$34.5 genes can be administered regionally or systemically to treat non-neurological tumors (see p. 3 of the response filed 3/17/03). Applicants contend in view of the teaching of the post-filed art, the instant invention would be enabled for the full scope encompassed by the claims.

In response, it is respectfully pointed out that the methods taught by Kooby and Walker encompass the administration of an HSV which has been modified such that neither of the two copies of the $\gamma_1$34.5 gene are expressed (i.e., both $\gamma_1$34.5 genes are knocked-out). Therefore, the methods taught by Kooby and Walker are different from the claimed method because the methods are drawn to the administration of different modified HSVs. The modified HSV used by Kooby and Walker comprise specific mutations (including the knock-out of both $\gamma_1$34.5 genes) which result in an HSV that has "attenuated neurovirulence" (see Kooby, p. 1326, first column) and which can replicate in rapidly dividing cells (i.e. cancer cells), but not in non-cancerous cells (e.g., see Kooby, p. 1326, first column and Walker, p. 2238, first paragraph).

However, the modified HSV of the instant claims has one intact $\gamma_1$34.5 gene, which would express the polypeptide encoded by the gene (ICP34.5). The modified HSV of the instant claimed method would be able to replicate in non-dividing cells (i.e. normal, non-cancerous cells). In fact, the prior art teaches that an HSV comprising a functional $\gamma_1$34.5 gene can replicate in non-cancerous cells, causing a number of manifestations of disease. Specifically, Whitely et al. (J. Clin. Invest. 1993, cited in the IDS as reference C112) teaches the HSV-1 (F)R vector, which comprises a reconstituted $\gamma_1$34.5 gene, could replicate in cells in vitro and when administered to animals by intranasal, ocular, and vaginal infection resulted in: 1) viral infection in the trigeminal ganglia and brain (within 3 days of intranasal infection), 2) significantly greater ocular disease by day 3 of infection including erythema, injection, corneal edema, and opacification of the cornea; and edema, intense erythema and numerous ulcerative lesions when administered intravaginally (see Whitley, p. 2839-2840). Therefore, the prior art of record indicates that modified HSVs comprising an active and functional $\gamma_1$34.5 gene can infect non-dividing cells and result in the disorders indicated above when administered regionally or systemically to an individual. The references cited by the Applicants are not persuasive because the HSVs used in the methods of the cited references are different from the HSV used in the claimed methods and the prior art recognizes a number of problems associated with HSVs similar to the one used in the claimed method (i.e. HSV expressing ICP34.5) that are not an issue with HSVs that do not express ICP34.5 (i.e. HSV with knock-outs of both $\gamma_1$34.5 genes, such as the ones used in the experiments of Kooby and Walker). Therefore, the rejection of the claims as previously set forth are appropriate and the rejection is not withdrawn.

6. Claims 1-9 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase, "only one γ1.34.5 gene remains **intact**." This recitation renders the claim indefinite because the term "intact" is unclear because it is not defined in the specification and it is unclear if a modification consisting of a conservative substitution would result in an "intact" $\gamma_1$34.5 gene.

Claims 2-9 are dependent claims and are rejected for the same reasons.

Response to Arguments

7. Applicant's arguments filed 3/17/03 have been fully considered but they are not fully persuasive. Applicants' arguments are sufficient to overcome the 112, second rejection of record with respect to the clarification of only one of the two γ_1.34.5 genes being intact and with respect to the typographical errors (i.e. "γ1 34.5 gene"). However, the Applicants have not set forth any arguments pertaining to the indefiniteness of the term "intact". Therefore, the rejection of the claims is not withdrawn.

Conclusion

No claim is allowed

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 26, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER